CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074560

Trade Name : FLURBIPROFEN TABLETS USP 100MG

Generic Name: Flurbiprofen Tablets USP 100mg

Sponsor : Warner Chilcott, Inc.

Approval Date: May 16, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074560

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074560

APPROVAL LETTER

ANDA 74-560

Warner Chilcott, Inc.
Attention: Norma Enders, R.Ph.
182 Tabor Road
Morris Plains, NJ 07950

MAY 16 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated November 9, 1994, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Flurbiprofen Tablets, USP, 100 mg.

Reference is also made to your amendments dated March 10 and March 25, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Flurbiprofen Tablets, USP, 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug Ansaid® Tablets, 100 mg of Pharmacia and Upjohn Co. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Doug Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074560

FINAL PRINTED LABELING

Each tablet contains:
Flurbiprofen, USP........100 mg

Usual Dosage–See package insert for complete product information.

Dispense in tight, light-resistant container, as defined in the USP.

Store at controlled room temperature 15°-30° C (59°-86° F).

Keep this and all drugs out of the reach of children.

Manufactured for:
WARNER CHILCOTT LABS
Div of Warner-Lambert Co. ©1995
Morris Plains, NJ 07950 USA
By: MOVA Pharmaceutical Corporation
Caguas, Puerto Rico 00725

N 0047-0462-24

Flurbiprofen Tablets, USP

100 mg

0462G000

Caution–Federal law prohibits dispensing without prescription.

APPROVED

100 Tablets

WARNER
CHILCOTT

FOR POSITION ONLY

N 0047-0462-24

Exp date and lot

MAY 16 1997

N 0047-0462-30

Each tablet contains:
Flurbiprofen, USP...100 mg

Usual Dosage–See package insert for complete product information.

Dispense in tight, light-resistant container, as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

Keep this and all drugs out of the reach of children.

Flurbiprofen Tablets, USP

100 mg

Caution–Federal law prohibits dispensing without prescription.

FOR POSITION ONLY

N 0047-0462-30

APPROVED

Exp date and lot

MAY 16 1997

0462G000

Manufactured for:
WARNER CHILCOTT LABS
Div of Warner-Lambert Co. ©1995
Morris Plains, NJ 07950 USA
By: MOVA Pharmaceutical Corporation
Caguas, Puerto Rico 00725

500 Tablets

WARNER
CHILCOTT

Flurbiprofen Tablets, USP
0462G000

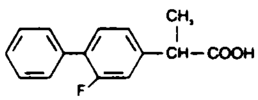
FOR POSITION ONLY

MAY 16 1997

Flurbiprofen Tablets, USP

DESCRIPTION

Flurbiprofen is a nonsteroidal anti-inflammatory agent. Flurbiprofen is a phenylalkanoic acid derivative designated chemically as (±)-2-(2-fluoro-4-biphenylyl) propionic acid. The molecular formula is $C_{15}H_{13}FO_2$, with a molecular weight of 244.26. Flurbiprofen is a white or slightly yellow crystalline powder. It is slightly soluble in water at pH 7.0 and readily soluble in most polar solvents. Its structural formula is:



Each tablet for oral administration contains 100 mg of flurbiprofen. In addition, each tablet contains the following inactive ingredients: Candelilla Wax, FCC; Colloidal Silicon Dioxide, NF; Croscarmellose Sodium, NF; FD&C Blue No. 2 Aluminum Lake; Hydroxypropyl Methylcellulose, USP; Lactose Monohydrate, NF; Magnesium Stearate, NF; Microcrystalline Cellulose, NF; Polyethylene Glycol, NF; Polysorbate 80, NF; and Titanium Dioxide, USP.

CLINICAL PHARMACOLOGY

Flurbiprofen is a nonsteroidal anti-inflammatory agent which has shown anti-inflammatory, analgesic, and antipyretic properties in pharmacologic studies. As with other such drugs, its mode of action is not known. However, it is a potent prostaglandin synthesis inhibitor, and this property may be involved in its anti-inflammatory effect.

Flurbiprofen is well absorbed after oral administration, reaching peak blood levels in approximately 1.5 hours (range 0.5 to 4 hours). Administration with food alters the rate of absorption but does not affect the extent of drug availability. The elimination half-life is approximately 6 hours with 90% of the half-life values from 3 to 9 hours. Individual half-life values ranged from 2.8 to 12 hours. There is no evidence of drug accumulation, and flurbiprofen does not induce enzymes that alter its metabolism. Excretion of flurbiprofen is 88% to 98% complete 24 hours after the last dose.

Flurbiprofen is extensively metabolized and excreted primarily in the urine, about 20% as free and conjugated drug and about 50% as hydroxylated metabolites. About 90% of the flurbiprofen in urine is present as conjugates. The major metabolite, 4'-hydroxy-flurbiprofen, has been detected in human plasma, but in animal models of inflammation this metabolite showed little anti-inflammatory activity. Flurbiprofen is more than 99% bound to human serum proteins.

In a reported study the average maximum serum concentration of flurbiprofen, following a 100 mg oral dose of flurbiprofen tablets in normal volunteers (n=184), was 15.2 μg/mL, with 90% of the values between 10 and 22 μg/mL. In geriatric subjects (n=7) between the ages of 58 and 77 years, 100 mg flurbiprofen resulted in an average peak drug level of 18.0 μg/mL and an average elimination half-life of 6.5 hours (range 3 to 10 hours). In geriatric rheumatoid arthritis patients (n=13) between the ages of 65 and 83 years receiving 100 mg flurbiprofen, the average maximum blood level was 12.7 μg/mL and the average elimination half-life was 5.6 hours (range 4 to 10 hours).

In a study assessing flurbiprofen pharmacokinetics in end stage renal disease (ESRD), mean urinary recovery of a 100 mg dose was 73% in 48 hours for 9 normal subjects and 17% in 96 hours for 8 ESRD patients undergoing continuous ambulatory peritoneal dialysis. Plasma concentrations of flurbiprofen were about 40% lower in the ESRD patients; the elimination half-life of flurbiprofen was unchanged. Elimination of the 4'-hydroxy-flurbiprofen metabolite was markedly reduced in the ESRD patients. The pharmacokinetics of flurbiprofen in patients with decreased renal function but not ESRD have not been determined.

The pharmacokinetics of flurbiprofen in patients with hepatic disease have not been determined.

The efficacy of flurbiprofen has been demonstrated in patients with rheumatoid arthritis and osteoarthritis. Using standard assessments of therapeutic response, flurbiprofen (200 to 300 mg/day) demonstrated effectiveness comparable to aspirin (2000 to 4000 mg/day), ibuprofen (2400 to 3200 mg/day), and indomethacin (75 to 150 mg/day).

In patients with rheumatoid arthritis, flurbiprofen may be used in combination with gold salts or corticosteroids.

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INDICATIONS AND USAGE

Flurbiprofen tablets are indicated for the acute or long-term treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

CONTRAINDICATIONS

Flurbiprofen tablets are contraindicated in patients who have previously demonstrated hypersensitivity to the product. Flurbiprofen should not be given to patients in whom flurbiprofen, aspirin, or other nonsteroidal anti-inflammatory drugs induce asthma, urticaria, or other allergic-type reactions. Fatal asthmatic reactions have been reported in such patients receiving this type of drug.

WARNINGS

Risk of Gastrointestinal (GI) Ulcerations, Bleeding and Perforation with Nonsteroidal Anti-inflammatory Therapy
Serious gastrointestinal toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with nonsteroidal anti-inflammatory drugs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with nonsteroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms. In patients observed in clinical trials of such agents for several months to two years, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3 to 6 months, and in about 2 to 4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various nonsteroidal anti-inflammatory agents in causing such reactions. High doses of any such agent probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to off-set the potential increased risk of GI toxicity.

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

PRECAUTIONS

General Precautions

Impaired Renal or Hepatic Function: As with other nonsteroidal anti-inflammatory drugs, flurbiprofen should be used with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Studies to assess the pharmacokinetics of flurbiprofen in patients with decreased liver function have not been done.

Renal Effects: Toxicology studies in rats have shown renal papillary necroses at dosage levels equivalent on a mg/kg basis to those used clinically in humans. Similar findings were seen in monkeys given high doses (50 to 100 mg/kg, or approximately 20 to 40 times the human therapeutic dose) for 90 days.

In clinical studies, kidney function tests were done at least monthly in patients taking flurbiprofen. In these studies, renal effects of flurbiprofen were similar to those seen with other nonsteroidal anti-inflammatory drugs.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is typically followed by recovery to the pretreatment state. Those patients at high risk who chronically take flurbiprofen should have renal function monitored if they have signs or symptoms that may be consistent with mild azotemia, such as malaise, fatigue, loss of appetite, etc. Occasionally patients may develop some elevation of serum creatinine and BUN levels without signs or symptoms.

The elimination half-life of flurbiprofen was unchanged in patients with end stage renal disease (ESRD). Flurbiprofen metabolites are primarily eliminated by the kidneys and elimination of 4'-hydroxy-flurbiprofen was markedly reduced in ESRD patients. Therefore, patients with significantly impaired renal function may require a reduction of dosage to avoid accumulation of flurbiprofen metabolites and should be monitored. (See also the CLINICAL PHARMACOLOGY section.)

Liver Tests: As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may disappear with continued therapy. The ALT (SGPT) test is probably the most sensitive indicator of liver injury. Meaningful (3 times the upper limit of normal) elevations of ALT or AST (SGOT) have been reported in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with flurbiprofen.

Anemia: Anemia is commonly observed in rheumatoid arthritis and is sometimes aggravated by nonsteroidal anti-inflammatory drugs, which may produce fluid retention or minor gastrointestinal blood loss in some patients. Therefore, patients who have initial hemoglobin values of 10 g/dL or less, and who are to receive long-term therapy, should have hemoglobin values determined periodically.

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Fluid Retention and Edema: Fluid retention and edema have been reported; therefore, flurbiprofen should be used with caution in patients with cardiac decompensation, hypertension, or similar conditions.

Vision Changes: Blurred and/or diminished vision has been reported with the use of flurbiprofen and other nonsteroidal anti-inflammatory drugs. Patients experiencing eye complaints should have ophthalmologic examinations.

Effect on Platelets and Coagulation: Flurbiprofen inhibits collagen-induced platelet aggregation. Prolongation of bleeding time by flurbiprofen has been demonstrated in humans after single and multiple oral doses. Patients who may be adversely affected by prolonged bleeding time should be carefully observed when flurbiprofen is administered.

Information for Patients: Flurbiprofen, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Nonsteroidal anti-inflammatory drugs are often essential agents in the management of arthritis, but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections) and likely benefits of nonsteroidal anti-inflammatory drug treatment, particularly when the drugs are used for less serious conditions where treatment without such agents may represent an acceptable alternative to both the patient and the physician.

Drug Interactions

Antacids: Administration of flurbiprofen tablets to volunteers under fasting conditions, or with antacid suspension, yielded similar serum flurbiprofen-time profiles in young subjects ($n=12$). In geriatric subjects ($n=7$) there was a reduction in the rate but not the extent of flurbiprofen absorption.

Anticoagulants: Flurbiprofen, like other nonsteroidal anti-inflammatory drugs, has been shown to affect bleeding parameters in patients receiving anticoagulants, and serious clinical bleeding has been reported. The physician should be cautious when administering flurbiprofen to patients taking anticoagulants.

Aspirin: Concurrent administration of aspirin and flurbiprofen resulted in 50% lower serum flurbiprofen concentrations. This

Flurbiprofen Tablets, USP

effect of aspirin (which also lowers serum concentrations of other nonsteroidal anti-inflammatory drugs given with it) has been demonstrated in patients with rheumatoid arthritis (n=15) as well as normal volunteers (n=16). Concurrent use of flurbiprofen and aspirin is therefore not recommended.

Beta-adrenergic Blocking Agents: The effect of flurbiprofen on blood pressure response to propranolol and atenolol was evaluated in men with mild uncomplicated hypertension (n=10). Flurbiprofen pretreatment attenuated the hypotensive effect of a single dose of propranolol but not atenolol. Flurbiprofen did not appear to affect the beta-blocker-mediated reduction in heart rate. Flurbiprofen did not affect the pharmacokinetic profile of either drug, and the mechanism underlying the interference with propranolol's hypotensive effect is unknown. Patients taking both flurbiprofen and a beta-blocker should be monitored to ensure that a satisfactory hypotensive effect is achieved

Cimetidine, Ranitidine: In normal volunteers (n=9), pretreatment with cimetidine or ranitidine did not affect flurbiprofen pharmacokinetics, except that a small (13%) but statistically significant increase in the area under the serum concentration curve of flurbiprofen resulted with cimetidine.

Digoxin: Studies of concomitant administration of flurbiprofen and digoxin to healthy men (n=14) did not show a change in the steady state serum levels of either drug.

Diuretics: Studies in normal volunteers have shown that flurbiprofen, like other nonsteroidal anti-inflammatory drugs, can interfere with the effects of furosemide. Although results have varied from study to study, effects have been shown on furosemide-stimulated diuresis, natriuresis, and kaliuresis. Other nonsteroidal anti-inflammatory drugs that inhibit prostaglandin synthesis have been shown to interfere with thiazide diuretics in some studies, and with potassium-sparing diuretics. Patients receiving flurbiprofen and furosemide or other diuretics should be observed closely to determine if the desired effect is obtained.

Oral Hypoglycemic Agents: In one study, flurbiprofen was given to adult diabetics who were already receiving glyburide (n=4), metformin (n=2), chlorpropamide with phenformin (n=3), or glyburide with phenformin (n=6). Although there was a slight reduction in blood sugar concentrations during concomitant administration of flurbiprofen and hypoglycemic agents, there were no signs or symptoms of hypoglycemia.

Carcinogenesis, Mutagenesis, Impairment of Fertility
An 80-week study in mice at doses of 2, 5, and 12 mg/kg/day and a 2-year study in rats at doses of 0.5, 2, and 4 mg/kg/day did not show evidence of carcinogenicity at maximum tolerated doses of flurbiprofen.

Flurbiprofen did not impair the fertility of male or female rats treated orally at 2.25 mg/kg/day for 65 days and 16 days, respectively, before mating.

Pregnancy: *Teratogenic Effects:* Pregnancy Category B
In teratology studies flurbiprofen, given to mice in doses up to 12 mg/kg/day, to rats in doses up to 25 mg/kg/day, and to rabbits in doses up to 7.5 mg/kg/day, showed no teratogenic effects

Because there are no adequate and well-controlled studies in pregnant women, and animal teratology studies do not always predict human response, flurbiprofen is not recommended for use in pregnancy.

Labor and Delivery: Flurbiprofen's effects on labor and delivery in women are not known. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats treated throughout pregnancy. Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), use of flurbiprofen during late pregnancy is not recommended.

Nursing Mothers: Concentrations of flurbiprofen in breast milk and plasma of nursing mothers suggested that a nursing infant could receive approximately 0.10 mg flurbiprofen per day in the established milk of a woman taking 200 mg/day. Because of possible adverse effects of prostaglandin-inhibiting drugs on neonates, flurbiprofen is not recommended for use in nursing mothers.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Adverse reaction information was derived from patients who received flurbiprofen in blinded-controlled and open-label clinical trials, and from worldwide marketing experience and from publications. In the description below, rates of the more common events (greater than 1%) and many of the less common events (less than 1%) represent clinical study results. For rarer events that were derived principally from worldwide marketing experience and the literature (printed in *italics*), accurate rate estimates are generally impossible.

Of the 4123 patients in premarketing studies, 2954 were treated for at least 1 month, 1448 for at least 3 months, 948 for at least 6 months, 356 for at least 1 year, and 100 for at least 2 years. Of the 4123 patients, 9.4% dropped out of the studies because of an adverse drug reaction, principally involving the gastrointestinal tract (5.8%), central nervous system and special senses (1.4%), skin (0.6%), and genitourinary tract (0.5%).

Incidence Greater Than 1%
An asterisk after a reaction identifies reactions which occurred in 3 to 9% of patients treated with flurbiprofen. Reactions occurring in 1 to 3% of the patients are unmarked.

Gastrointestinal: Dyspepsia*, diarrhea*, abdominal pain*, nausea*, constipation, GI bleeding, flatulence, elevated liver enzymes, and vomiting.

Central Nervous System: Headache*, nervousness, and other manifestations of CNS "stimulation" (e.g., anxiety, insomnia, reflexes increased, and tremor), and symptoms associated with CNS "inhibition" (e.g., amnesia, asthenia, somnolence, malaise, and depression).

Respiratory: Rhinitis.

Dermatological: Rash

5

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Respiratory: Rhinitis

Dermatological: Rash

Special Senses: Dizziness, tinnitus, and changes in vision.

Genitourinary: Signs and symptoms suggesting urinary tract infection*.

Body as a Whole: Edema*.

Metabolic/Nutritional: Body weight changes.

Incidence Less Than 1%
(Causal Relationship Probable)

The reactions listed in this category occurred in <1% of patients in the clinical trials or were reported during postmarketing experience from other countries. Adverse reactions reported only in worldwide postmarketing experience or the literature (which presumably indicates that they are rarer) are italicized.

Gastrointestinal: Peptic ulcer disease (see also **WARNINGS, Risk of Gastrointestinal (GI) Ulcerations, Bleeding and Perforation with Nonsteroidal Anti-inflammatory Therapy**), gastritis, bloody diarrhea, stomatitis, esophageal disease, hematemesis, and hepatitis; *cholestatic and non-cholestatic jaundice*.

Central Nervous System: Ataxia, cerebrovascular ischemia, confusion, paresthesia, and twitching.

Hematologic: Decrease in hemoglobin and hematocrit, iron deficiency anemia, *hemolytic anemia*, and *aplastic anemia*; leukopenia; eosinophilia; ecchymosis and *thrombocytopenia*. (See also **PRECAUTIONS, Effect on Platelets and Coagulation**.)

Respiratory: Asthma and epistaxis.

Dermatological: Angioedema, urticaria, eczema, and pruritus; *photosensitivity, toxic epidermal necrolysis*, and *exfoliative dermatitis*.

Special Senses: Conjunctivitis and parosmia.

Genitourinary: Hematuria and renal failure; *interstitial nephritis*.

Body as a Whole: Chills and fever; *anaphylactic reaction*.

Metabolic/Nutritional: Hyperuricemia.

Cardiovascular: Heart failure, hypertension, vascular diseases, and vasodilation.

Incidence Less Than 1%
(Causal Relationship Unknown)

The following reactions have been reported in patients taking flurbiprofen under circumstances that do not permit a clear attribution of the reaction to flurbiprofen. These reactions are being included as alerting information for physicians. Adverse reactions reported only in worldwide postmarketing experience or the literature (which presumably indicates that they are rarer) are italicized.

Gastrointestinal: Periodontal abscess, appetite changes, cholecystitis, and dry mouth.

Central Nervous System: Convulsion, meningitis, hypertonia, cerebrovascular accident, emotional lability, and subarachnoid hemorrhage.

Hematologic: Lymphadenopathy.

Respiratory: Bronchitis, laryngitis, dyspnea, pulmonary embolism, pulmonary infarct, and hyperventilation.

Dermatological: Alopecia, nail disorder, herpes simplex, zoster, dry skin, and sweating.

Special Senses: Ear disease, corneal opacity, glaucoma, retrobulbar neuritis, changes in taste, and transient hearing loss; *retinal hemorrhage*.

Genitourinary: Menstrual disturbances, vaginal and uterine hemorrhage, vulvovaginitis, and prostate disease.

Metabolic/Nutritional: Hyperkalemia.

Cardiovascular: Arrhythmias, angina pectoris, and myocardial infarction

Musculoskeletal: Myasthenia.

DRUG ABUSE AND DEPENDENCE

No drug abuse or drug dependence has been observed with flurbiprofen.

OVERDOSAGE

Information on overdosage is available for 13 children and 12 adults. Nine of the 13 children were less than 6 years old. Drowsiness occurred after doses of 150 to 800 mg in 3 of these young children (with dilated pupils in 1), and in a 2-year-old who also had semiconsciousness, pinpoint pupils, diminished tone, and elevated liver enzymes. Other children who ingested doses of 200 mg to 2.5 g showed no symptoms.

Among the adults, a 70-year-old man with a history of chronic obstructive airway disease died. Toxicological analysis showed acute flurbiprofen overdose and a blood ethanol concentration of 100 mg/dL. In the other cases, symptoms were as follows: coma and respiratory depression after 3 to 6 g; drowsiness, nausea, and epigastric pain after 2.5 to 5 g; epigastric pain and dizziness after 3 g; headache and nausea after ≤ 2 g; agitation after 1.5 g; and drowsiness after 1 g. One patient, who took 200 to 400 mg flurbiprofen and 2.4 g fenoprofen, had disorientation and diplopia. Three adults had no symptoms after 3 to 5 g flurbiprofen.

Treatment of an overdose: The stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Supportive treatment should be instituted as necessary. Some patients have been given supplemental oral or intravenous fluids and required no other treatment.

In mice, the flurbiprofen LD_{50} was 750 mg/kg when administered orally and 200 mg/kg when administered intraperitoneally. The primary signs of toxicity were prostration, ataxia, loss of righting reflex, labored respiration, twitches, convulsions, CNS depression, and splayed hind limbs. In rats, the flurbiprofen LD_{50} was 160 mg/kg when administered orally and 400 mg/kg when administered intraperitoneally. The primary signs of toxicity were tremors, convulsions, labored respiration, and prostration. These were observed mostly in the intraperitoneal studies.

DOSAGE AND ADMINISTRATION

Flurbiprofen tablets are administered orally.

Rheumatoid arthritis and osteoarthritis: Recommended starting

12 adults. Nine of the 13 children were less than 6 years old. Drowsiness occurred after doses of 150 to 800 mg in 3 of these young children (with dilated pupils in 1), and in a 2-year-old who also had semiconsciousness, pinpoint pupils, diminished tone, and elevated liver enzymes. Other children who ingested doses of 200 mg to 2.5 g showed no symptoms.

Among the adults, a 70-year-old man with a history of chronic obstructive airway disease died. Tomicological analysis showed acute flurbiprofen overdose and a blood ethanol concentration of 100 mg/dL. In the other cases, symptoms were as follows: coma and respiratory depression after 3 to 6 g; drowsiness, nausea, and epigastric pain after 2.5 to 5 g; epigastric pain and dizziness after 3 g; headache and nausea after ≤ 2 g; agitation after 1.5 g; and drowsiness after 1 g. One patient, who took 200 to 400 mg flurbiprofen and 2.4 g fenoprofen, had disorientation and diplopia. Three adults had no symptoms after 3 to 5 g flurbiprofen.

Treatment of an overdose: The stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Supportive treatment should be instituted as necessary. Some patients have been given supplemental oral or intravenous fluids and required no other treatment.

In mice, the flurbiprofen LD_{50} was 750 mg/kg when administered orally and 200 mg/kg when administered intraperitoneally. The primary signs of toxicity were prostration, ataxia, loss of righting reflex, labored respiration, twitches, convulsions, CNS depression, and splayed hind limbs. In rats, the flurbiprofen LD_{50} was 160 mg/kg when administered orally and 400 mg/kg when administered intraperitoneally. The primary signs of toxicity were tremors, convulsions, labored respiration, and prostration. These were observed mostly in the intraperitoneal studies.

DOSAGE AND ADMINISTRATION

Flurbiprofen tablets are administered orally.

Rheumatoid arthritis and osteoarthritis: Recommended starting dose is 200 to 300 mg total daily dose administered BID, TID, or QID. (Most experience in rheumatoid arthritis has been with TID or QID dosage.) The largest recommended single dose in a multiple-dose daily regimen is 100 mg. The dose should be tailored to each patient according to the severity of the symptoms and the response to therapy.

Although a few patients have received higher doses, doses above 300 mg per day are not recommended until more clinical experience with flurbiprofen is obtained.

HOW SUPPLIED

Flurbiprofen Tablets, USP, 100 mg (blue, round, unscored film-coated tablets, debossed with "WC462" on one side and plain on the other side) are supplied as follows:

N 0047-0462-24	Bottles of 100
N 0047-0462-30	Bottles of 500

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in tight, light-resistant container, as defined in the USP.

Caution: Federal law prohibits dispensing without prescription.

Issued November 1995

Manufactured for:
WARNER CHILCOTT LABS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA
By: MOVA Pharmaceutical Corporation
Caguas, Puerto Rico 00725
0462G000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074560

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.4

2. ANDA # 74-560

3. NAME AND ADDRESS OF APPLICANT

Warner Chilcott
Attention: Norma Enders, R.Ph.
182 Tabor Road
Morris Plains, NJ 07950

4. BASIS OF SUBMISSION
Patent expiry

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Flurbiprofen

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

November 9, 1994: Submission
March 10, 1997: Amendment
March 25, 1997: Amendment
Amendments are being reviewed in this review cycle.

10. PHARMACOLOGICAL CATEGORY
NSAID

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s):

13. DOSAGE FORM

Tablets

14. POTENCY

100 mg (50 mg is withdrawn per amendment dated 12.7.95)

16. RECORDS AND REPORTS: N/A

18. CONCLUSIONS AND RECOMMENDATIONS: Approvable

See Comments Section.

19. REVIEWER:

Dave Gill

DATE COMPLETED:

April 15, 1997

HFD-623/D.Gill/ 4-15-97 4/21/97
HFD-623/V.Sayeed/
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F/T by
APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074560

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA #74-560 SPONSOR: Warner Chilcott
DRUG: flurbiprofen
DOSAGE FORM: tablet
STRENGTHS/(s): 100 & 50 mg
TYPE OF STUDY: Single X Multiple Fasting X Fed X

STUDY SUMMARY:

Fasting: Twenty-six subjects enrolled, 24 completed (13 in sequence 1, 11 in sequence 2), no serious adverse events. Randomized, single dose, two-way crossover, 2 week washout. Log-transformed 90% CI's: AUC0-t, 97-102; AUCINF, 97-102; CMAX, 90-120.
ISSUES:
1) S1, test, had the first nonzero concentration was CMAX. Excluded, 90% CI's recalculated: AUC0-t, 96.8-102.0; AUCINF, 96.8-101.8; CMAX, 87.8-117.8
2) Statistically significant period effects ($p < 0.05$) occurred for AUC0-t, AUCINF, and their log-transformed values:
- no nonzero predose concentrations, washout > 30 half-lives (longest t½ was 11 hr, 336 hr / 11 hr = 30.5)
- no evidence of variation in sample processing or analysis
- frozen stability documented
- no evidence of induction or inhibition from parent drug or metabolite
- equal residual effects?

Fed: All 18 subjects enrolled completed the study, no serious adverse events. Randomized, single dose, three treatment, six sequence, three period design (actually six periods) with 14-30 day washout. There were three groups based on dates of dosing (Group 1 = 15 subjects, Group 2 = 2 subjects, Group 3 = 1 subject). Based on pooled data, the ratios of least squares geometric means were: AUC0-t, 0.989; AUCINF, 0.987; CMAX, 1.081. Comparison of test fed vs. test fasting: AUC0-t decreased about 10% with food; CMAX decreased about 17% with food; TMAX increased about 27% with food. These results are consistent with the labeling.
ISSUES:
1) Data was analyzed as follows:
- pooled without regard to dosing date (N = 18)
- Group 1 data only (N = 15)
- coding for periods revised to account for different dosing dates

In all cases the ratios were within the 0.8-1.2 limits.
2) S11 was included in violation of the protocol (consumption of an NSAID within 7 days of starting). Ratios were recalculated for all the conditions above excluding S11, and were still within 0.8-1.2.

WAIVER/DISSOLUTION: Dissolution testing was acceptable for both 100 and 50 mg strengths and conducted according to USP conditions. With regard to core components, the two strengths are qualitatively identical and the % compositions relative to core weights are very similar.

PRIMARY REVIEWER: James D. Henderson, Ph.D. BRANCH: II
INITIAL:_____________ DATE 6-1-95

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D BRANCH: II
INITIAL:_____________ DATE 6/2/95

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith K. Chan, Ph.D.
INITIAL:_____________ DATE 6/5/95

ASSOCIATE DIRECTOR, OFFICE OF GENERIC DRUGS: Lawrence J. Lesko, Ph.D
INITIAL:_____________ DATE 6/28/95

FLURBIPROFEN - WARNER CHILCOTT, ANDA #74-560, FOOD STUDY

Design:

			4/9	4/23	5/7	5/9	5/21	5/23
Group	Subj.	N			Period			
1	1-6,8-16	15	1	2	3			
2	17,18	2		1	2		3	
3	7	1	1			2		3

Summary of Ratios of Least Squares Geometric Means:

Condition	N	AUC0-t	AUCINF	CMAX
1	18	0.9892	0.9874	1.081
2	15	0.9884	0.9862	1.077
3	17	0.9895	0.9876	1.066
4	14	0.9886	0.9863	1.052
5	18	0.9862	0.9843	1.057
6	17	0.9864	0.9844	1.033

Condition:

1 Sponsor's reported values using pooled data from all 18 subjects

2 Condition 1 excluding Subjects 7, 17, and 18

3 Condition 1 excluding Subject 11

4 Condition 2 excluding Subject 11

5 Reviewer's analysis using revised coding for periods

6 Condition 5 excluding Subject 11

JUN 5 1995

Flurbiprofen
100 & 50 mg tablet
ANDA #74-560
Reviewer: James D. Henderson
File: 74560SDW.N94

Warner Chilcott
Morris Plains, NJ
Submitted:
November 9, 1994 &
May 8, 1995 &
May 24, 1995

REVIEW OF FASTING AND FED BIOEQUIVALENCE STUDIES, DISSOLUTION DATA, AND A WAIVER REQUEST

Background

On 1/25/94 the sponsor submitted bioequivalence study protocols for fasting and fed studies of its test product flurbiprofen tablets 100 mg. These protocols (#94-004) were reviewed by the Division (file date 3/8/94) and found acceptable as long as the firm incorporated several recommendations. The sponsor was so informed by letter on 3/15/94.

The sponsor has now submitted the results of fasting and fed bioequivalence studies comparing its test product flurbiprofen 100 mg tablets with the reference listed drug (RLD) Ansaid® (Upjohn, NDA #18-766, 10/31/88). In addition, the sponsor has submitted a request for waiver of in vivo biostudy requirements for its lower strength test product flurbiprofen 50 mg tablets and dissolution data for both strengths. The submission was received by the reviewer on 3/16/94.

On 4/24/95 and 5/23/95 the sponsor was requested to submit additional information (transcripts of conversations attached). These amendments were submitted on 5/8/95 and 5/24/95.

The Division issued a revised guidance for flurbiprofen tablets (2/4/94) which describes the clinical pharmacology and pharmacokinetics of this drug.

I. FASTING STUDY

A. Study Sites

Clinical:
Principal Investigator:
Medical Director:
Protocol #: 9141-5001 (11/24/93; amended 1/20/94, 3/10/94, and 3/17/94); final IRB approval 3/23/94
Dosing Dates: Period 1, 4/23/94; Period 2, 5/7/94
Analytical:
Analytical Director:
Analysis Dates: 5/24/94 through 6/15/94

B. Study Design

This was a single dose, randomized, two-treatment, two-way crossover study in 24 healthy male subjects comparing the sponsor's test product flurbiprofen 100 mg tablets with the reference product Ansaid® (Upjohn) under fasting conditions with a two week washout between treatments.

C. Subject Selection

Twenty-six healthy male subjects (24 subjects plus two alternates) were enrolled into the study after signing IRB-approved informed consent. If all 26 subjects enrolled complete the study, then all samples would be assayed. If a subject drops out, an alternate of that sequence would replace the dropped subject. No additional add-on subjects would be dosed after the study has started without the sponsor's consent.

Inclusion Criteria:

- male, 18-50 years old
- within ± 10% from normal weight for height and frame[1]
- good health as determined by medical history, physical examination, laboratory values (hematology, serum chemistry, urinalysis), and urine drug abuse screen
- no Rx medications for two weeks prior and no OTC medications, vitamins, or unusual diet for one week prior to study start and until after the final blood draw

Exclusion Criteria:

- clinically abnormal physical examination suggesting an abnormality of any organ system
- any clinically significant abnormal laboratory value
- numerous known allergies, or known allergy to flurbiprofen, aspirin, NSAIDS, or any component of Ansaid® or flurbiprofen (WC) tablets
- history of asthma or urticaria precipitated by aspirin or any other NSAID
- history of alcohol or drug dependency or drug abuse
- receipt of an investigational drug within 28 days of screening
- received a RX drug or has been treated within four weeks prior to study screening for a condition which precludes enrollment
- blood donation or blood loss of > 200 mL within four weeks prior to screening

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[1] Table of Desirable Weights of Adults, Metropolitan Life Insurance Company, 1983.

I. Study Procedures

Treatments:

After a supervised overnight fast (10 hr), each subject received one of the following treatments:

1) Trt. A (test), flurbiprofen tablet, 1 X 100 mg, Warner Chilcott lot #JT12801, use by 12/95; batch size assay, 96.4%; manufactured 12/14/93

2) Trt. B (ref.), Ansaid® tablet, 1 X 100 mg, Upjohn lot #474YP, exp 1/98; assay, 95.7%

Each dose was taken with 240 mL of water. Immediately after dosing, the subject's oral cavity was checked to confirm the tablet and fluid were swallowed. After a two week washout, each subject received the alternative treatment.

Restrictions:

Subjects were confined to the clinical facility from at least 10 hours before dosing until 48 hours postdose. Subjects abstained from caffeine- and xanthine-containing products, and from alcohol for at least two days prior to dosing days and until after the last sample was collected. Subjects were active for the first four hours postdose and were not permitted to lie down or sleep. No strenuous exercise was permitted during the study. Smoking was not prohibited.

Meals and Fluids:

Subjects fasted for at least 10 hours before dosing and for four hours after dosing when standardized meals began. Water was restricted for two hours postdose but was allowed freely at all other times. Subjects were instructed not to eat or drink any unusual foods or liquids during dosing.

Blood Sampling:

Venous blood samples (10 mL) were collected into anticoagulated EDTA) evacuated glass tubes at 0 (predose), 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, 18, 24, 36, and 48 hours postdose. Blood samples were centrifuged and the plasma separated and stored frozen at -20° pending shipment to the analytical site. After arrival at the site, samples were stored at -20° until assayed.

Note: Although the protocol specified that the plasma samples were to be divided into two portions (the first set shipped on dry ice, and the second set shipped after safe arrival of the first set), the samples were shipped as one set.

E. Analytical Methodology and Data Analysis

Analytical:

Pharmacokinetics:

The following pharmacokinetic parameters were determined:

- area under the plasma concentration-time curve to the last quantifiable concentration (AUC) by the linear trapezoidal rule.
- area under the curve extrapolated to infinity (AUCINF) calculated by adding C_t/KE to AUCTLQC, where C_t is the last quantifiable concentration and KE is the elimination rate constant
- maximum observed plasma concentration (CMAX)
- time to maximum plasma concentration (TMAX)
- terminal elimination rate constant (KE) obtained from the slope of the line through the terminal points fitted by linear least squares regression; no values earlier than 6 hr after dosing were used in view of biphasic elimination for flurbiprofen
- half-life (THALF) = 0.693/KE

Statistics:

Statistical analyses were performed using the GLM procedure of SAS. The statistical model contained main effects of sequence, subject(sequence), period, and treatment. Sequence effects were tested against the mean square term for subject(sequence); all other main effects were tested against the mean square error term (statistical significance if $p < 0.05$).

F. Results

Product Information:

1. **Formulation**: see Table 1

2. **Potency**: The potencies of the test and reference biostudy products were 96.4% and 95.7%, respectively, and are within ± 5% of each other.

3. **Batch Size**: The batch size is stated as tablets.

4. **Dissolution**: see Table 2. The results are acceptable.

Clinical:

5. **Completion**: Twenty-six subjects (24 plus 2 alternates) were enrolled, and 24 subjects completed the study:

- S2 withdrew after Period 1 on his own request.
- S23 failed to report for Period 2.

6. **Adverse Events**: Four subjects reported five adverse events: 1) nausea (probably related to dosing, test); 2) lightheadedness (possibly related, ref.); 3) nervousness; 4) sore throat; 5) musculoskeletal pain. All events were judged to be of mild intensity and required no treatment.

7. **Protocol Deviations**: In three cases, actual collection times differed from the scheduled times by ≥ 7%; actual times were used in calculations for these samples. There was one missed sample (S3, Per. 1, 2.33 hr, difficulty with heparin lock) and parameters were "calculated around the missing value". The reviewer's AUC calculation agreed with the sponsor's reported value.

Pharmacokinetics/Statistics:

8. **Plasma Concentrations**: see Table 3. There were no instances of nonzero predose concentrations. There was only one case where CMAX was the first nonzero concentration (S1, Per. 1, Trt. A).

9. **Pharmacokinetic Parameters**: see Table 4. The study was unbalanced with 13 subjects in Sequence 1 and 11 subjects in Sequence 2. There were statistically significant ($p < 0.05$) period effects for AUC0-t, AUCINF, and their log-transformed values (see Comment 3 below).

10. **T/R ratios** are shown in Table 5.

<u>Analytical</u>:

G. Comments

1. The sponsor's reported 90% CI's for log-transformed AUC0-t, AUCINF, and CMAX are shown in Table 4. The reviewer repeated the SAS analyses with the diskette provided by the sponsor and obtained similar results to the sponsor's rounded values.

Since S1 had CMAX as the first nonzero concentration for Trt. A, the SAS analysis was repeated with S1 deleted, and 90% CI's were as follows: logAUC0-t, 96.8-102.0; logAUCINF, 96.8-101.8; logCMAX, 87.8-117.8.

2. Based on visual appearance, in two cases the reviewer

The reviewer repeated the SAS analysis for logAUCINF using the revised KEL value for S13, Trt. 2, and deleting S17, Trt. 2. The 90% CI for logAUCINF was 96.6-101.3.

3. Statistically significant ($p < 0.05$) period effects were noted for AUC0-t, AUCINF, and their log-transformed values. It is unlikely that the period effects are due to carryover for two reasons: 1) there were no nonzero predose concentrations; 2) washout was adequate with minimum numbers of 63 and 62 drug half-lives for Trts. A and B, respectively. The sponsor also notes that there are no reports of self-inhibition of biotransformation for flurbiprofen.

4. Additional pharmacokinetic parameters are shown in Table 7.

5. There were seven reassayed samples (6 anomalous values, and 1 missing original value) from three subjects. In two of these cases, the reported (median) value agrees closely with the original value, and in one case there was no original value so the single repeat value was used.

In the remaining four cases, the original value was considered to be anomalous, or a pharmacokinetic outlier. Based on the concentrations at the flanking times, the reviewer concurs with the reported (median) values in these four cases

6. The sponsor chose the weighting factor 1/PHR for linear regression analysis of standard curves. Using the approach of Bolton[2] to examine whether a weighted linear regression is required, the reviewer used the raw PHR data from all of the standard curves as follows:

- For each standard concentration (CONC), the mean PHR, SD, CV, variance ($\sigma = SD^2$), and INVVAR ($= 1/\sigma$) were calculated.

- Heterogeneity of variance is demonstrated if either the variance of the dependent variable mean PHR (σ_{MPHR}) or the standard deviation (SD) is proportional to the independent variable (CONC).

- From the REG procedure of SAS, the R^2 value for σ_{MPHR} vs. CONC was 0.88, indicating fair correlation. If σ is proportional mean PHR, then 1/CONC or 1/PHR might be an appropriate weighting factor.

- The R^2 value for SD vs. CONC was 0.9308 (good correlation), and the R^2 values for CV vs. MPHR and CV vs. CONC were 0.0253 and 0.0278, respectively (no correlation, slope was

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2 Bolton S. Pharmaceutical statistics: practical and clinical applications. 2nd ed. New York: Marcel Dekker, Inc., 1990:234-5.

not significantly different from zero), indicating a constant CV model. For the constant CV model, 1/CONC² or 1/PHR² might be an appropriate weighting factor.

- The weighting factor should be inversely proportional to variance. The R^2 values for INVVAR (= 1/σ) vs. 1/CONC (WF1), 1/CONC² (WF2), 1/PHR (WF3), and 1/PHR² (WF4) were 0.7993, 0.6158, 0.8054, and 0.6253, respectively, suggesting that WF1 (1/CONC) and WF3 (1/PHR) have the best inverse correlations with variance.

- The R^2 values for MPHR vs. CONC with the following weighting factors were:

    1) 1/CONC - 0.9999
    2) 1/CONC² - 0.9999
    3) 1/PHR - 0.9999
    4) 1/PHR² - 0.9999

- The reviewer's results show that the data appear to be described by a constant CV model. However, the best inverse correlations with variance are for the weighting factors 1/CONC and 1/PHR.

II. FOOD STUDY

A. Study Sites

Clinical:
Principal Investigator:
Medical Director:
Protocol #: 9141-5002 (11/24/93; amended 1/20/94, 3/10/94, and 3/17/94); final IRB approval 3/23/94
Dosing Dates: Group I: Period 1, 4/9/94; Period 2, 4/23/94; Period 3, 5/7/94
Group II: Period 1, 4/23/94; Period 2, 5/7/94; Period 3, 5/21/94
Group III: Period 1, 4/9/95; Period 2, 5/9/95; Period 3, 5/23/95
Analytical:
Analytical Director:
Analysis Dates: 6/3/94 through 6/21/94

B. Study Design

This was a single dose, randomized, three-treatment, three-period, six-sequence crossover study in 18 healthy male subjects comparing the sponsor's test product flurbiprofen 100 mg tablets under fed conditions with 1) the reference product Ansaid® (Upjohn) under fed conditions, and 2) the test product under fasting conditions, with a 14-30 day washout between treatments.

Dosing dates for the three periods differed as follows, in order to accommodate college exams to prevent dropouts:

			4/9	4/23	5/7	5/9	5/21	5/23
Group	Subj.	N			Period			
1	1-6,8-16	15	1	2	3			
2	17,18	2		1	2		3	
3	7	1	1			2		3

C. Subject Selection

Eighteen healthy male subjects were enrolled into the study after signing IRB-approved informed consent. Inclusion/Exclusion criteria were the same as for the fasting study.

D. Study Procedures

Treatments:

After a supervised overnight fast (10 hr), each subject received one of the following treatments:

1) Trt. A (test, fed), flurbiprofen tablet, 1 X 100 mg, Warner Chilcott lot #JT12801, use by 12/95

2) Trt. B (test, fasting), flurbiprofen tablet, 1 X 100 mg, Warner Chilcott lot #JT12801, use by 12/95

3) Trt. C (ref., fed), Ansaid® tablet, 1 X 100 mg, Upjohn lot #474YP, exp 1/98

Each dose was taken with 240 mL of water. Immediately after dosing, the subject's oral cavity was checked to confirm the tablet and fluid were swallowed. In two subsequent dosings, and after 14-30 day washout periods, each subject received the alternative treatments.

Subjects receiving Treatments A and C were fed a standard high-fat breakfast prior to dosing, were required to consume the entire meal in thirty minutes, and were then immediately dosed. The meal consisted of one fried egg, one buttered English muffin, one slice of American cheese, one slice of Canadian bacon, one serving of hash brown potatoes, 180 mL of orange juice, 240 mL of whole milk.

Restrictions: same as in fasting study

Meals and Fluids: same as in fasting study

Blood Sampling: same as in fasting study, except for shipping (see Results, Analytical section below)

E. Analytical Methodology and Data Analysis

Same as for fasting study, except that only one set of subject samples were assayed per analytical run.

F. Results

Product Information: same as in fasting study

Clinical:

1. **Completion**: Eighteen subjects were enrolled, and all 18 subjects completed the study.

2. **Adverse Events**: Six subjects reported twelve adverse events. All events were judged to be of mild intensity and required no treatment. Four of the 12 events were judged as possibly related to the study drug: anxiety, insomnia, restlessness (S4, test, fed); headache (S8, test, fed). Other adverse events judged not related to drug administration included rash, nervousness, rhinitis, syncope, and conjunctivitis.

3. **Protocol Deviations**:

- All 18 subjects were not dosed together (see Study Design above, and Comment #3 below)

- In one case (S3, Trt. C, 0.25 hr, 2 min late), the actual collection time differed from the scheduled times by > 7%; the actual time was used in calculations for this sample.

- In three cases, subjects took unauthorized medications during unsupervised periods:

  - S8, 1 Comtrex® tablet 8 days before Period 2 dosing
  - S17, 2 ASA tablets 325 mg 12 and 13 days prior to Period 1 dosing
  - S11, 2 ibuprofen caplets 400 mg and 1 Entex® tablet 4 days prior to Period 1 dosing

  Due to the short half-lives of these medications, the sponsor assumed adequate washout and allowed the subjects to participate. However, the IRB-approved protocol, Section VII. D. (p. 127 of the submission) states that "Subjects must be informed that if aspirin or any NSAID is consumed from 7 days before the first dosing until after the last blood sample is collected, they will be dropped from the study". This inclusion requirement is repeated in the Clinical Report (p. 1480 of the submission). Therefore, the inclusion of S11 was a protocol violation, and, in the reviewer's opinion, S11 should have been excluded.

- The protocol was amended to inform subjects that they would be dropped from the study if any NSAID was used within seven days of study start. In the amendment, the sponsor acknowledges that this change was not implemented into the case report forms.

<u>Pharmacokinetics/Statistics</u>:

4. **Plasma Concentrations**: see Table 8. The sponsor reported the pooled data from all 18 subjects with no distinction between dosing groups. There were no instances of nonzero predose

concentrations. There were no cases where CMAX was the first nonzero concentration.

5. **Pharmacokinetic Parameters**: see Tables 9 and 10. The sponsor reported the results as a balanced study with 3 subjects per dosing sequence. There were no statistically significant (p > 0.05) period or treatment effects or sequence (p > 0.1) effects for AUC0-t, AUCINF, CMAX, and their log-transformed values. The sponsor also recalculated the study including only the 15 subjects from Group 1. Table 10 shows the least squares means and the ratios of geometric means from the Group 1 analysis. The reviewer confirmed the sponsor's results in both cases.

Analytical:

G. Comments

1. The inclusion of S11 was a protocol violation. The reviewer repeated the SAS analysis after excluding S11, using all pooled data (N = 17) and only Group 1 data (N = 14). For N = 17, the ratios of least squares geometric means were: AUC0-t, 0.9895; AUCINF, 0.9876; CMAX, 1.066. For N = 14: AUC0-t, 0.9886; AUCINF, 0.9863; CMAX, 1.052. (See Table 11, Conditions 3 and 4)

2. Based on the number of dosing days, there were actually six periods in this study. For example, Group 1 subjects would have periods coded 1, 2, and 3. Group 2 subjects would have periods

coded 2, 3, and 5, based on the calendar days on which dosing occurred. Group 3 would have periods coded 1, 4, and 6. The reviewer made these changes and repeated the SAS analysis. The results are shown in Table 11 as Conditions 5 and 6. In all cases, the ratios of geometric least squares means were within the acceptance limits of 0.8-1.2.

3. The reviewer used the raw PHR data from all of the standard curves as follows for analysis of the weighting factor selection:

- From the REG procedure of SAS, the R^2 value for σ_{PHR} vs. CONC was 0.9278, indicating good correlation. If σ is proportional to mean PHR, then 1/CONC or 1/PHR might be an appropriate weighting factor.

- The R^2 value for SD vs. CONC was 0.9986 (strong correlation), and the R^2 values for CV vs. MPHR and CV vs. CONC were 0.1915 and 0.1913, respectively (no correlation, slope was not significantly different from zero), indicating a constant CV model. For the constant CV model, $1/CONC^2$ or $1/PHR^2$ might be appropriate weighting factors.

- The weighting factor should be inversely proportional to variance. The R^2 values for INVVAR (= $1/\sigma$) vs. 1/CONC (WF1), $1/CONC^2$ (WF2), 1/PHR (WF3), and $1/PHR^2$ (WF4) were 0.9849, 0.9567, 0.9818, and 0.9623, respectively, suggesting that WF1 (1/CONC) and WF3 (1/PHR) have the best inverse correlations with variance.

- The R^2 values for MPHR vs. CONC with the following weighting factors were:

  1) 1/CONC - 1.0
  2) $1/CONC^2$ - 0.9998
  3) 1/PHR - 1.0
  4) $1/PHR^2$ - 0.9998

- The reviewer's results show that the data appear to be described by a constant CV model. However, the weighting factors 1/CONC and 1/PHR are most strongly inversely correlated with variance.

6. The current labeling (PDR, 49th ed., 1995, p. 2520) for Ansaid® (Upjohn) states that "administration with food alters the rate of absorption but does not affect the extent of drug availability". From Table 9 (N = 18), the % differences for Trt. A (test, fed) vs. Trt. B (test, fasting) indicate that AUC0-t was decreased about 10% in the presence of food. CMAX was decreased about 17% and TMAX was increased about 27% in the presence of food. These changes are consistent with the qualitative description in the labeling. Reported data indicates that CMAX may be decreased 27-32% with food (refer to Division guidance).

III. WAIVER REQUEST

1. The sponsor states that its lower strength test product flurbiprofen 50 mg tablets is proportionally similar in active and inactive ingredients to the higher strength 100 mg tablet used in the fasting and fed bioequivalence studies. Based on formulation and comparable dissolution of the test products to the corresponding strengths of the innovator products, the sponsor requests waiver from bioequivalence study requirements under 21 CFR Part 320.22(d)(2) for the 50 mg strength.

2. Table 1 shows the formulations of the 100 and 50 mg strengths of the test product. Three of the excipients are exactly proportional as a % core tablet weight, and two other excipients are very similar.

IV. RECOMMENDATIONS

1. The bioequivalence study (fasting conditions) conducted by Warner Chilcott on its flurbiprofen 100 mg tablet, lot #JT12801, comparing it to Ansaid® 100 mg tablet, lot #474YP, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Warner-Chilcott's flurbiprofen 100 mg tablet is bioequivalent under fasting conditions to the reference product Ansaid® 100 mg tablet manufactured by Upjohn.

2. The bioequivalence study (fed conditions) conducted by Warner Chilcott on its flurbiprofen 100 mg tablet, lot #JT12801, comparing it to Ansaid® 100 mg tablet, lot #474YP, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Warner-Chilcott's flurbiprofen 100 mg tablet is bioequivalent under fed conditions to the reference product Ansaid® 100 mg tablet manufactured by Upjohn.

3. The dissolution testing conducted by Warner Chilcott on its flurbiprofen 100 mg tablet, lot #JT12801, is acceptable and should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of pH 7.2 phosphate buffer at 37° using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

> Not less than   of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. The dissolution testing conducted by Warner Chilcott on its flurbiprofen 50 mg tablet, lot #JT12091, is acceptable. The firm has conducted acceptable in vivo bioequivalence studies under fasting and fed conditions (submitted 11/9/94 and 5/8/95) comparing its 100 mg tablet of the test product with the 100 mg tablet of the reference product Ansaid® manufactured by Upjohn. The formulation for the 50 mg strength is proportionally similar with respect to active and inactive ingredients to the 100 mg strength of the test product that underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 50 mg strength of the test product is granted. The 50 mg tablet of the test product is therefore deemed bioequivalent to the 50 mg tablet of Ansaid® manufactured by Upjohn.

5. From the bioequivalence point of view, the firm has met the requirements of _in vivo_ bioequivalence and _in vitro_ dissolution testing and the application is acceptable.

James D. Henderson, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK ____________ 6/2/95

Concur: ____________ Date ____________
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

JDH/crc/6-1-95/74-560

cc: ANDA #74-560 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Patnaik, Henderson), Drug File, Division File

Table 1 - Test Product Formulations

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	Ingredient	mg tablet	% core weight	mg tablet	% core weight
CORE	flurbiprofen, USP	100.00	25	50.00	16.67
	lactose monohydrate, NF				
	colloidal silicon dioxide, NF				
	croscarmellose sodium, NF				
	microcrystalline cellulose, NF				
	magnesium stearate, NF				
	Total Core Weight (mg)	400.00	-	300.00	-
COAT	Blue				
	White				
	Purified Water, USP	*			
Polish	Candelilla Wax,				
	Purified Water, USP				

* does not appear in final product

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): flurbiprofen
Dose Strength: 100 & 50 mg
ANDA No.: 74-560
Firm: Warner-Chilcott
Submission Date: 11/9/94
File Name: 74560SDW.N94

I. Dissolution Testing (USP Conditions):

USP 23 Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: pH 7.2 phosphate buffer Volume: 900 mL
Specifications: NLT / 45 min
Reference Drug: Ansaid® (Upjohn)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot #JT12801 Strength (mg) 100			Reference Product Lot #474YP Strength (mg) 100 exp 1/98		
	Mean %	Range	%CV	Mean %	Range	%CV
10	84		3.3	84		3.0
20	87		1.3	88		2.7
30	89		1.7	91		2.5
45	92		1.3	93		2.8
60	92		1.3	93		3.0

Sampling Times (Minutes)	Test Product Lot #JT12091 Strength (mg) 50			Reference Product Lot #005YY Strength (mg) 50 exp 1/98		
	Mean %	Range	%CV	Mean %	Range	%CV
10	83		4.6	84		5.9
20	88		2.1	89		5.4
30	90		2.5	91		4.0
45	91		2.3	92		3.8
60	92		2.1	93		3.2

Table 3 - Mean Reported Plasma Concentrations of Flurbiprofen (Fasting Study, N = 24)

Time (hr)	Trt. A Mean (ug/mL)	Test CV (%)	NC *	Trt. B Mean (ug/mL)	Ref. CV (%)	Upjohn *	% diff.
0	0	-	0	0	-	0	-
0.25	3.49	106	24	2.48	120	21	40.73
0.5	6.90	64	24	4.48	94	24	54.02
0.75	8.31	57	24	5.49	89	24	51.37
1	9.33	50	24	6.55	76	24	42.44
1.25	9.96	46	24	7.07	65	24	40.88
1.5	10.6	45	24	8.03	60	24	32.01
1.75	10.5	42	24	8.95	51	24	17.32
2	10.1	39	24	9.01	46	24	12.10
2.33	9.60	34	24	9.23	44	23	4.01
2.67	8.85	33	24	9.26	43	24	-4.43
3	8.26	33	24	8.63	44	24	-4.29
3.5	7.55	35	24	7.93	33	24	-4.79
4	7.17	31	24	8.25	35	24	-13.09
6	4.37	33	24	4.75	34	24	-8.00
8	2.94	37	24	3.34	38	24	-11.98
10	2.31	46	24	2.58	40	24	-10.47
12	1.67	57	24	1.89	52	24	-11.64
18	0.79	75	24	0.85	59	24	-7.06
24	0.42	93	23	0.43	76	23	-2.33
36	0.09	210	8	0.10	194	10	-10.00
48	0.02	397	2	0.02	490	1	0.00

* number of nonzero concentrations

one missing sample (S3, Per. 1)

Trt. A = flurbiprofen tablet, 1 X 100 mg, Warner-Chilcott
Trt. B = Ansaid® tablet, 1 X 100 mg, Upjohn

Table 4 - Mean Reported Pharmacokinetic Parameters of Flurbiprofen (Fasting Study, N = 24)

units: AUC's, µg*hr/mL; CMAX, µg/mL)

Parameter	Trt. A Mean	(test) CV (%)	Trt. B Mean	(ref.) CV (%)		90% CI
AUCT						
Arith.	74.4	29	75.2	30	-	-
LSM	74.1	-	74.7	-	-0.80	97-102
lnAUCT	-	-	-	-	0.993	97-102
AUCINF						
Arith.	76.2	30	77.1	31	-	-
LSM	75.9	-	76.6	-	-0.91	97-102
lnAUCINF	-	-	-	-	0.992	97-102
CMAX						
Arith.	13.5	27	12.9	23	-	-
LSM	13.5	-	12.8	-	5.47	92-117
lnCMAX	-	-	-	-	1.03	90-120
TMAX (hr)	1.82	77	2.49	63	-26.91	-
KEL (hr^{-1})	0.136	19	0.135	20	0.74	-
HALF (hr)	5.33	26	5.37	27	-0.74	-

For TMAX, KEL, and HALF, arithmetic means are reported.
LSM = least squares mean
For untransformed parameters, the <u>% difference</u> is calculated as follows: % diff. = (T - R) * 100 / R, using the least squares means. For log-transformed parameters, the <u>T/R ratio of geometric means</u> is calculated as exp(logT -log R), where the quantity (logT -logR) is the estimate from the ANOVA.

Trt. A = flurbiprofen tablet, 1 X 100 mg, Warner-Chilcott
Trt. B = Ansaid® tablet, 1 X 100 mg, Upjohn

Table 5 - Reported T/R Ratios (Fasting Study)

Subject	AUC	AUCINF	CMAX
1			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
24			
25			
26			
< 75%	0	0	5
75-125%	24	24	13
> 125%	0	0	6

Table 6 - Prestudy Validation Results

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Table 7 - Additional PK Parameters (Fasting Study)

Parameter:	RATIO[1]		NUMHALF[2]	
	Trt. A	Trt. B	Trt. A	Trt. B
Mean	0.977	0.975	5.389	5.488
CV (%)	0.92	1.12	12.7	14.8
Range	0.954-0.989	0.953-0.990	4.34-7.306	4.24-7.775

[1] RATIO = AUC0-t / AUCINF
[2] NUMHALF = TLAST / HALF

Trt. A = flurbiprofen (WC); Trt. B = Ansaid® (Upjohn)

Table 8 - Mean Reported Plasma Concentrations of Flurbiprofen (Fed Study, N = 18)

Time (hr)	Trt. A (test, fed) Mean (µg/mL) (CV%, *)	Trt. B (test, fasting) Mean (µg/mL) (CV%, *)	Trt. C (ref., fed) Mean (µg/mL) (CV%, *)	% diff. (A v. C)
0	0.0 (-,0)	0.0 (-,0)	0.0 (-,0)	-
0.25	0.83 (218,8)	3.33 (130,17)	0.34 (233,7)	144.12
0.5	3.12 (158,18)	7.01 (91,18)	2.03 (131,18)	53.69
0.75	4.94 (115,17)	8.06 (67,18)	3.77 (100,17)	31.03
1	6.24 (88,18)	8.83 (49,18)	5.32 (76,18)	17.29
1.25	7.02 (73,18)	9.79 (39,18)	7.21 (64,18)	-2.64
1.5	7.82 (54,18)	10.75 (36,18)	8.31 (53,18)	-5.90
1.75	8.59 (42,18)	11.02 (35,18)	8.7 (38,18)	-1.26
2	9.02 (41,18)	10.64 (30,18)	9.32 (26,18)	-3.22
2.33	8.99 (33,18)	10.16 (29,18)	9.09 (22,18)	-1.10
2.67	8.46 (27,18)	10.03 (18,18)	8.49 (15,18)	-0.35
3	8.23 (25,18)	9.82 (22,18)	8.25 (14,18)	-0.24
3.5	7.8 (23,18)	8.48 (23,18)	7.81 (14,18)	-0.13
4	7.04 (23,18)	7.71 (24,18)	7.18 (16,18)	-1.95
6	4.46 (25,18)	4.41 (31,18)	4.69 (26,18)	-4.90
8	3.06 (32,18)	3.02 (35,18)	3.24 (31,18)	-5.56
10	2.39 (41,18)	2.36 (43,18)	2.44 (36,18)	-2.05
12	1.73 (49,18)	1.72 (52,18)	1.75 (44,18)	-1.14
18	0.85 (67,18)	0.85 (74,18)	0.88 (74,18)	-3.41
24	0.48 (85,18)	0.49 (92,18)	0.49 (83,18)	-2.04
36	0.13 (155,9)	0.14 (138,8)	0.13 (170,9)	0.00
48	0.05 (234,4)	0.05 (257,4)	0.04 (287,3)	25.00

* Number of nonzero concentrations

Trt. A = flurbiprofen (Warner-Chilcott, fed), 1 X 100 mg tablet
Trt. B = flurbiprofen (Warner-Chilcott, fasting), 1 X 100 mg tablet
Trt. C = Ansaid® (Upjohn, fed), 1 X 100 mg tablet

Table 9 - Mean Reported Pharmacokinetic Parameters of Flurbiprofen (Fed Study, N = 18)

Parameter	Trt. A - mean (CV%)	Trt. B - mean (CV%)	Trt. C - mean (CV%)	% Diff. (A v. C)	% Diff. (A v. B)
AUC0-t[1]	71.4 (31)	79.4 (28)	72.0 (31)	-0.83	-10.08
AUCINF	73.1 (32)	81.3 (29)	73.9 (32)	-1.08	-1.08
CMAX (μg/mL)	11.9 (27)	14.4 (15)	10.8 (21)	10.19	-17.36
TMAX (hr)	2.14 (60)	1.68 (53)	2.30 (44)	-6.96	27.38
KEL (hr^{-1})	0.126 (28)	0.125 (25)	0.125 (26)	0.80	0.80
HALF (hr)	5.98 (32)	5.99 (32)	5.99 (31)	-0.17	-0.17

Table 10 - Least Squares Means and Ratios of Flurbiprofen (Fed Study)

Parameter	Trt. A - LSMean	Trt. C - LSMean	Ratio[2] (A vs.C)
N = 18			
AUC0-t[1]	71.36	71.95	0.992
logAUC0-t	-	-	0.9892
AUCINF	73.13	73.86	0.99
logAUCINF	-	-	0.9874
CMAX (μg/mL)	11.89	10.8	1.10
logCMAX	-	-	1.081
N = 15			
AUC0-t	74.34	74.97	0.9916
logAUC0-t	-	-	0.9884
AUCINF	76.21	77.01	0.9896
logAUCINF	-	-	0.9862
CMAX (μg/mL)	11.90	10.86	1.095
logCMAX	-	-	1.077

1 units for AUC's: μg*hr/mL

2 For untransformed parameters, Ratio = Trt. A_{LSM} / Trt. C_{LSM}. For log-transformed parameters, Ratio = exp(logA - logC), where (logA - logC) is the estimate from the ANOVA.

Trt. A = flurbiprofen (Warner-Chilcott, fed), 1 X 100 mg tablet
Trt. B = flurbiprofen (Warner-Chilcott, fasting), 1 X 100 mg tablet
Trt. C = Ansaid® (Upjohn, fed), 1 X 100 mg tablet

Table 11 - Summary of Ratios of Least Squares Geometric Means (Fed Study)

Condition	N	AUC0-t	AUCINF	CMAX
1	18	0.9892	0.9874	1.081
2	15	0.9884	0.9862	1.077
3	17	0.9895	0.9876	1.066
4	14	0.9886	0.9863	1.052
5	18	0.9862	0.9843	1.057
6	17	0.9864	0.9844	1.033

Condition:

1 Sponsor's reported values using pooled data from all 18 subjects

2 Condition 1 excluding Subjects 7, 17, and 18

3 Condition 1 excluding Subject 11

4 Condition 2 excluding Subject 11

5 Reviewer's analysis using revised coding for periods

6 Condition 5 excluding Subject 11